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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,479	03/28/2005	Nils Brunner	59866.000004	8086

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EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,479	BRUNNER ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005 and 06 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☒ Claim(s) *4-25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 3/28/2005 and 2/6/2007. Claims 1-25 are pending. Claims 1-3 are under examination in the instant Office action.

Specification

The disclosure is objected to because of the following informalities: the specification lacks a section entitled "Brief Description of the Drawings" which includes a description for each figure of the drawings.

Appropriate correction is required.

Claim Objections

Claims 4-25 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Priority

Receipt is acknowledged of an executed declaration as well as an unexecuted declaration, both filed on 3/28/2007, as well as an ADS filed on the same date. It is noted for the record that the executed oath filed 3/28/2007 contains a foreign priority claim only to PA200201430 (filed September 29, 2002) whereas both the unexecuted declaration and ADS filed claim priority to two Danish foreign priority documents: PA200201430 (filed September 29, 2002) and DK199900476 (filed April 9, 1999). Receipt is also acknowledged of a status inquiry on 6/12/2006 in which Applicant states that because an unexecuted declaration was filed on 3/28/2005, the Notice of Acceptance of Application Under 35 U.S.C. 371 and 37 C.F.R. 1.495 ("Notice") dated 9/29/2005 appears to be in error. Applicant appears to believe that because an unexecuted oath was supplied *along with* the executed oath, the PCT application was improperly accepted into the National Stage in the United States. However, due to the presence of a properly executed declaration in the papers filed 3/28/2005, the Notice sent 9/29/2005 was not in error.

However, Applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in Denmark on April 9, 1999 cannot be granted since the United States (PCT) application was filed more than twelve months thereafter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, and therefore dependent claims 2-3, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 recites "[a] method for detecting and/or screening and/or monitoring a cancer in an individual, said method comprising determining a first parameter represented by the concentration of TIMP-1 in at least one excreta from the individual, wherein the presence of the first parameter above a predetermined discrimination value is an indication that the individual has a high likelihood of either having a cancer or progression in a cancer" in lines 1-8 (emphasis added). Claim 1 is vague and indefinite in that the phrase "wherein the presence of the first parameter above a predetermined discrimination value is an indication that the individual has a high likelihood of either having a cancer or progression in a cancer" is unclear for at least two reasons. First, the metes and bounds of a "predetermined discrimination value" are unclear because it is

not clear how such a value would be determined. Furthermore, without any knowledge with regard to how such a value would be determined, the metes and bounds of the value itself are unclear. Second, the term "high likelihood" in claim 1 is a relative term which renders the claim indefinite. The term "high likelihood" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, does Applicant consider a 30% chance of having cancer a "high likelihood" or does Applicant consider, e.g., only percentages greater than 80% as indicative that an individual has a "high likelihood" of having cancer?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The instant claims are drawn to a method of detecting and/or screening and/or monitoring a cancer in an individual comprising determining a first parameter (e.g., the concentration of TIMP-1 in at least one excreta from the individual), wherein the presence of the first parameter above a predetermined discrimination value is an indication that the individual has a high likelihood of either having a cancer or cancer progression. Claim 2 is limited to such a method wherein the cancer is selected from the group comprising breast, prostate, colorectal, cervical, ovarian, lung, pancreatic, renal, vulvar and hepatocellular carcinomas, minimal residual disease and recurrent cancer. Claim 3 is limited to such a

method wherein the excretum is saliva. Together the claims encompass a method for diagnosing *any* type of cancer in an individual. The claims require the determination of a single parameter, wherein said parameter corresponds to the concentration of TIMP-1 in a sample of excreta, including, but not limited to a sample of urine, saliva, feces, and lacrimal and sudoriferous gland secretions (i.e., tears and sweat). The claims require that if the determined parameter (i.e., the concentration of TIMP-1 in at least one excreta) is above a predetermined "discrimination value", the individual or patient has a "high" likelihood of either having cancer or cancer progression. It is not clear from the claims how the "discrimination value" is determined. The invention is complex in that it involves measuring the concentration of a gene expression product in any excreta of the body of an individual to detect the presence or progression of any cancer present anywhere in the body of the tested individual. The nature of the invention requires knowledge of a correlation between the concentration of any TIMP-1 expression product and the presence of or predisposition to any form of cancer.

Breadth of the claims: The claims are extremely broad in that they encompass the measurement of any TIMP-1 expression product in any excreta of the body to diagnose or monitor

progression of any cancer. The large breadth of the claims exacerbates the complexity of the invention.

Guidance of the specification/The existence of working examples: Applicant concedes in the specification that "serum studies have shown that there is no significant difference between the total TIMP-1 concentrations in serum samples from individuals having colorectal cancer and healthy blood donors, most properly because the platelets will leak TIMP-1 during coagulation *in vitro*" (see specification at page 4, lines 25-29). The specification also discloses that the concentration of TIMP-1 in urine and plasma from the same colorectal cancer patients have also been evaluated, but without finding any noticeable correlation since no TIMP-1 elevation was found in the urine (Brünner, unpublished data)" (paragraph bridging pages 4-5). However, Applicant teaches that TIMP-1 can be used to detect and/or monitor cancer in an individual "as it has surprisingly been found by the inventors that the TIMP-1 protein can be detected in human excreta, such as saliva in unexpected high concentrations with respect to the TIMP-1 concentration in plasma" (see specification at page 7, lines 4-8). The examples disclosed in the specification are drawn to the results of assays from three patients groups (I-III) wherein saliva was obtained from 8 apparently healthy donors and three patients

with known colorectal cancer. Total TIMP-1 concentration as determined by ELISA were determined and compared to total TIMP-1 concentration in the plasma of the same patients. For all study participants, TIMP-1 levels in saliva were found to "correspond" to TIMP-1 levels in plasma (see page 17,line 11 to page 18, line 18 and page 19, lines 1-15). TIMP-1 levels were elevated in all three colorectal patients (page 19, lines 19-24). Based on these results, and on the fact that it has previously been found that a highly statistical difference has been found in the total plasma TIMP-1 values between colorectal cancer patients compared to total plasma TIMP-1 values of healthy individuals, Applicant concludes that "total TIMP-1 measurements in saliva can be used as a screening procedure to aid in identifying patients with a high risk of having colorectal cancer" (see page 20, lines 11-13). Applicant teaches away from the instantly claimed invention in Example 5 wherein Applicant discloses that "no statistical significant difference in total TIMP-1 plasma levels" was found between pre-operative plasma samples from 322 patients with primary breast cancer compared with 108 plasma samples from healthy blood donors (see paragraph bridging pages 21-22). Similarly, Example 7 teaches that free TIMP-1 in plasma alone is also not likely to be useful as a screening marker to identify patients with a high risk of having colorectal cancer

(see page 22, lines 29-34). Thus, it is unclear how TIMP-1 levels in excreta could be indicative of any cancer or any cancer progression, even if TIMP-1 saliva concentrations are correlative with TIMP-1 plasma levels.

The specification fails to provide a single working example of the claimed invention.

The specification fails to provide any guidance/examples with regard to the use of TIMP-1 concentration levels in excreta other than saliva to predict the likelihood of cancer or cancer progression.

The specification does not teach how elevated the level of TIMP-1 in the saliva of an individual must be in order to determine whether an individual is more or less likely to have cancer or cancer progression.

The specification does not provide any statistical analysis of the concentration of TIMP-1 in excreta of patients vs. healthy donors for any cancer other than colorectal cancer.

Predictability of the art/State of the art: The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics,

including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 - Discussion). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (*The Scientist* **18**(24):20, 20 Dec 2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

With specific regard to the use of TIMP-1 as a marker, Zhou et al (*Cancer Epidemiology, Biomarkers and Prevention* 7: 109-112, 1998) teach "analysis of TIMP-1 serum levels revealed

significant increases in pancreatic cancer patients, but TIMP-1 by itself was inadequate as a serum marker for cancer" (abstract). Oberg et al (*Anticancer Research* **20**: 1085-1091, 2000) teach that analyses of the total concentration of TIMP-1 in serum samples acquired from colorectal patients reveal that TIMP-1 is of limited value for tumor staging and prognosis (abstract). Oberg et al also teach that "wide, overlapping ranges" of concentrations are observed, which serves to preclude the usefulness of analyses of TIMP-1 and other measured factors. Furthermore, Michael et al (*Journal of Clinical Oncology* **17**: 1802-1808, 1999) teach that in contrast to the premise for the usefulness of the invention, TIMP-1 is largely absent from small-cell lung cancer specimens and that *decreased* tumoral expression of TIMP-1 rather than increased expression has prognostic significance.

Amount of experimentation necessary: Given the complex nature of invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. Even for claims specifically reciting the use of saliva and colorectal cancer, one would have to establish that TIMP-1 levels were predictive of cancer in a statistically significant sampling of patients and not simply correlative to

TIMP-1 plasma levels. Such an undertaking would include analysis of the different concentration levels of TIMP-1 in saliva of healthy individuals and cancer patients. One would then have to establish that elevated TIMP-1 concentration in the saliva is correlated with the presence of colorectal cancer and perform studies that prove a correlation with the TIMP-1 concentration levels and a predisposition to or development of colorectal cancer.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-3 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3 of copending Application No. 10/470,658. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-26 of copending Application No. 10/470,658. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-3 encompass, and thus anticipate, the embodiments recited in claims 4-26. The instant claims are drawn to methods for

detecting and/or screening and/or monitoring any cancer in an individual comprising determining the concentration of TIMP-1 in at least one excreta from the individual. As such the claims encompass the method claims of the 10/470,658 Application which are also drawn to such methods, but which further comprise limitations drawn to such methods wherein e.g., the concentration of TIMP-1 determined is the total concentration of TIMP-1 (claim 4), wherein the method further comprises the testing of a second parameter representing the concentration of a cancer marker other than TIMP-1 (claims 8-12), and wherein the concentration of TIMP-1 is determined by means of an immunoassay or an active assay.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all

patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Joseph Woitach can be reached at (571) 272-0739.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

June 22, 2007

DAVID GUZO
PRIMARY EXAMINER